PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
ABL-008-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BE 03/00190	07.11.2003	08.11.2002

International Patent Classification (IPC) or both national classification and IPC
C07K16/42

Applicant
ABLYNX N.V.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the opinion
   II ☐ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☒ Lack of unity of invention
   V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.06.2004	22.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Alconada Rodriguez, Telephone No. +49 30 25901-326

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/BE 03/00190

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-103 as originally filed

Claims, Numbers

1-51 received on 07.12.2004 with letter of 01.12.2004

Drawings, Sheets

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-14, 46-51 (in part), 17-45 (complete) and 1-8, 15 and 16 (with respect to industrial applicability)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-14, 46-51 (in part), 17-45 (complete) and 1-8, 15 and 16 (with respect to industrial applicability)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☒ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-14 and 46-51 (in part) and 15-16 (complete) .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	1-16, 46-51
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-16, 46-51
Industrial applicability (IA)	Yes:	Claims	9-14,46-51
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-8, 15 and 16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

This authority agrees with the International Search Authority (ISA) in that the present application contains 11 inventions which are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT for the following reasons.

The application relates to different antibody sequences. The common concept underlying the plurality of antibody sequences is that they are all single domain antibodies. Single domain antibodies are known in the prior art. For instance, Muyldermans, S. (2001) Reviews in molecular biotechnology, 74:277-302 describes methods for the isolation of single domain antibodies from camelidae (see figure 5) and provides references to prior art documents which report the isolation of single domain antibodies against different antigens (see table 1). In light of this prior art the above mentioned common concept is not novel and the problem underlying the present application can be redefined as the provision of additional single domain antibodies. The sequences identified in inventions 1 to 11 are different solutions to this problem. Due to the fact that single domain antibodies are known in the prior art and due to the fact that no other technical feature can be distinguished which, in the light of the prior art, could be regarded as a special technical feature in the sense of Rule 13.2 PCT due to the essential differences in the primary structures and on the nature of the of antigens recognised by the claimed single domain antibodies, there is no single general inventive concept underlying the plurality of claimed inventions of the present application in the sense of Rule 13.1 PCT. Consequently, the application does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

The applicant has requested the preliminary examination to be carried out on invention 2 (anti-TNF-alpha camelidae VHH antibodies and uses thereof) corresponding to present claims 1-14, 46-51 (in part) and 15 and 16 (complete) (previous claims 11-24 and 58-63 (in part) and 25 and 26 (complete)).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: WO 91/02078 A (PEPTIDE TECHNOLOGY LTD) 21 February 1991 (1991-02-21)

D2: MUYLDERMANS S: "SINGLE DOMAIN CAMEL ANTIBODIES: CURRENT STATUS" REVIEWS IN MOLECULAR BIOTECHNOLOGY, ELSEVIER, AMSTERDAM,, NL, vol. 74, no. 4, June 2001 (2001-06), pages 277-302, XP001057480 ISSN: 1389-0352

D1 discloses monoclonal antibodies against human TNF-alpha, including single domain antibodies (see page 4 lines 15-20) and the uses thereof for the treatment of diseases where it is desired to inhibit TNF-alpha activity (see page 4, lines 6-14). The single domain Ab to which D1 relates are those as defined by Ward et al. (Nature, 1989, 341:544-546) which relate to conventional ScFv consisting of the covalently-linked VH and VL regions of a monoclonal antibody, wherein the single domain antibodies of the present application relate to the variable region of the heavy chain of a camelidae antibody, which is naturally devoid of light chains. It appears that, even if the intention of the applicant was to obtain antibodies consisting of a single chain, the fact that the term "single domain antibodies" has been used in the prior art to relate to scFv antibodies results in a lack of novelty for the subject-matter of **claims 9-14 and 47-51**, which relate to the single domain antibodies as such, as well as for the subject-matter of **claims 1-8**, which relate to the uses of said antibodies.

In addition, the IPEA is of the opinion that the application lacks inventive step for the following reasons. D1, which can be considered as closest prior art, discloses different types of antibodies specific for TNF-alpha and their use as inhibitors of TNF-alpha activity.

The present application differs from the subject-matter of D1 in that the application uses anti-TNF-alpha camelidae VHH antibodies. Thus, the problem to be solved by the present application can be summarised as the provision of alternative monospecific anti-TNF-alpha antibodies. The problem is solved by the general VHH anti-TNF-alpha antibodies of claims 1-15 and by the specific VHH antibodies of SEQ ID NO:12-14 as defined in claim 16. The solution provided in the present application can not be considered as involving an inventive step since it was already known at the time of filing the application that camelidae VHH antibodies provide a convenient alternative to other types of monospecific antibodies (see D2, pages 280-290). These antibodies, due to their relative simple structure, show certain functional, technological and physico-chemical properties (see page 291, left-hand column, first paragraph) which would make then advantageous over other types of monospecific antibodies. Thus, the skilled person, when confronted with the above problem, would attempt to obtain camelidae anti-TNFalpha VHH antibodies as described in D2, thus arriving to the subject-matter of **claims 1-15**.

Moreover, the specific VHH molecules of SEQ ID NO:12-14 could only be considered to involve an inventive step if they show some unexpected or surprising properties. The applicants have provided evidence that the VHH antibody of SEQ ID NO:12 (TNF3E) shows an increased stability in the presence of pepsin (example 5), that the TNF3E antibody can be orally administered (example 6) and that the bivalent construct of SEQ ID NO:14 (consisting of TNF3E covalently linked to TNF3F) can be used for the treatment of chronic colitis (example 7). However, none of these properties provided in the examples can be considered as surprising with respect to what could be expected from the known properties of camelidae VHH antibodies described in the prior art (see list on page 291, left-hand column in D2). Thus, the skilled person, when obtaining camelidae anti-TNFalpha VHH according to the combined teaching of D1 and D2, would inevitably arrive to VHH molecules, which, if not identical to those of TNF3E and TNF3F, would show exactly the same properties. Therefore, no inventive step can be acknowledged for the subject-matter of claim 16, as far as it relates to the monomeric camelidae VHH of SEQ ID NO:12 and 13. Likewise, the use of two different VHH molecules to prepare bivalent mono- or bispecific VHH is also known from D2 (see figure 6) and thus, it would also be obvious for the skilled person to combine the non inventive monovalent anti-TNFalpha VHHs to obtain bivalent constructs as that of SEQ ID NO:14. Thus, **claim 16**, as far as it relates to the camelidae VHH of SEQ ID NO:14 is also devoid of an inventive step.

Claims 1-8 relates to different methods for the therapeutic administration of the anti-TNFalpha VHH to a subject. All the different methods relate to nothing else than a shopping list of all possible administration ways that are known from common pharmacology handbooks and for which no inventive step can be acknowledged if they do not involve the administration of a new and inventive compound. Likewise, **claims 9-14** relate to medical uses of the non-inventive polypeptides, where the compound is further described by its ability to pass through different biological barriers without being inactivated. These claims are identical in scope to claims 1-8 and are therefore also considered as to lack an inventive step.